



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number : **0 304 304 B1**

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification :  
**09.11.94 Bulletin 94/45**

(51) Int. Cl.<sup>5</sup> : **G01N 33/48**

(21) Application number : **88307657.2**

(22) Date of filing : **18.08.88**

(54) **Transdermal detection system.**

(30) Priority : **18.08.87 US 87699**

(43) Date of publication of application :  
**22.02.89 Bulletin 89/08**

(45) Publication of the grant of the patent :  
**09.11.94 Bulletin 94/45**

(84) Designated Contracting States :  
**CH DE ES FR GB IT LI NL SE**

(56) References cited :  
**EP-A- 0 154 664  
EP-A- 0 248 680  
WO-A-86/04680  
DE-A- 2 724 461  
GB-A- 2 054 844  
US-A- 4 595 011**

(73) Proprietor : **DERMAL SYSTEMS  
INTERNATIONAL  
6219 Poindexter Lane  
Rockville Maryland 20852 (US)**

(72) Inventor : **Peck, Carl C.  
6219 Poindexter Lane  
Rockville, MD 20852 (US)**

(74) Representative : **Charlton, Peter John et al  
Elkington and Fife  
Prospect House  
8 Pembroke Road  
Sevenoaks, Kent TN13 1XR (GB)**

**EP 0 304 304 B1**

Note : Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

## Description

The present invention relates to a transdermal detection system for the detection of a target substance which migrates to the surface of the skin of a subject by diffusion. More, particularly, the invention relates to a transdermal detection system which produces a detectable signal as the target substance migrates to the surface of the skin of the subject.

Various transdermal devices and systems are known for collecting and monitoring body fluids. For example, in Peck et al, "A Non-Invasive Transepidermal Toxicological Monitoring Device", Pittsburgh Conference and Exposition on Analytical Chemistry and Applied Spectroscopy, March 9, 1982, Meeting Abstracts Book, page 366, a transepidermal device is disclosed including an adhesive plastic chamber containing sodium chloride-impregnated absorbant pads and an activated charcoal impregnated disc for capturing a xenobiotic to prevent back transfer from the collection device into the body. The Peck copending application serial No. 660,778 filed February 11, 1985 discloses a dermal substance collection device including a liquid bridge transfer medium for transferring a dermal substance to a binding reservoir material which binds the substance and prevents back transfer loss of the substance from the collection device.

The Phillips U. S. patent No. 4,329,999 discloses a dermal patch for collecting sweat from a patient which includes a collecting pad for absorbing sweat. Similarly, the Phillips U.S. patent No. 4,595,011 discloses a transdermal dosimeter device including a dermal contact bridge, a fluid collecting component for collecting and storing fluids collected from the skin and a process component for binding or chemically converting the stored substances. The latter Phillips patent suggests that chemical conversion of collected substances to produce an observable color change in the device may be effected.

The Fogt et. al. U.S. patent No. 4,444,193 discloses an absorbent patch device for absorbing sweat, which patch device includes a chemical composition capable of reacting with chloride contained in the sweat.

The Pugliese U.S. patent No. 4,071,020 discloses an apparatus and methods for performing in-vivo measurements of enzyme activity wherein one or more reactants are placed directly on a predetermined area of the skin surface and are free to migrate into the skin. While the apparatus and methods of Pugliese are not dependent on collection of a substance such as sweat or interstitial fluid, they may be dangerous to the subject if the reactants have toxic effects upon migration into the skin of the subject.

Other devices are also known for measuring substances, particularly gases; in or emanating from the skin. For example, the Clark, Jr. U.S. patents Nos.

4,401,122 and 4,458,686 disclose apparatus and methods for measuring substances, particularly gases, which diffuse through the skin or are present underneath the skin in the blood or tissue using polarographic electrodes or enzyme electrodes. The Vestager et al U.S. patent No. 4,274,418 discloses an apparatus for measuring gases, for example oxygen and carbon dioxide, which diffuse from blood vessels and through skin tissue wherein the gas is directed to a measuring chamber in which the partial pressure is measured.

The present inventor has discovered that various substances migrate to the skin surface of a subject by diffusion in the absence of a liquid transport medium such as sweat and has discovered means for producing detectable signals in a transdermal detection system at the skin surface without direct placement of detector chemicals which are capable of migrating into the skin on the skin surface. Known transdermal devices rely on the collection of body fluids such as sweat or gaseous substances emanating from the skin or the binding of substances transferred through a liquid bridge transfer medium, without detection and signalling, or employ direct epidermal application of potentially toxic detector chemicals, and thus are disadvantageous for safely detecting and signaling substances which migrate to the skin surface of a subject by diffusion.

It is therefore an object of the present invention to provide a transdermal system for the detection of a substance which migrates to the skin surface of a subject by diffusion. It is a more specific object of the invention to provide a transdermal system for the detection of a substance which migrates to the skin surface of a subject by diffusion in the absence of a liquid medium such as sweat. It is a related object of the invention to provide a transdermal system for the detection of a substance which migrates to the surface of the skin of a subject by diffusion, which transdermal system does not rely on collecting a fluid from the skin surface and does not require direct placement of detector chemicals which can migrate into the skin on the skin surface in order to detect the target substance which has migrated to the skin surface of the subject.

These and additional objects are provided by the transdermal detection system according to the present invention which comprises an apparatus for detecting a target substance which has migrated to the surface of the skin of a subject by diffusion.

The invention provides an apparatus for the detection of a target substance which migrates to the surface of the skin of a subject by diffusion, comprising:

detector means including at least one detector chemical contained in solution and capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin

of the subject to produce a detectable signal; and attachment means for maintaining the detector means adjacent the surface of the skin of the subject; characterised in that:

the detector means further comprises a barrier means for substantially preventing said detector chemical from migrating into the skin of the subject, wherein the barrier means comprises either a microporous membrane containing covalent functional groups capable of covalently binding with the detector chemical contained in solution, or a permeable or a semipermeable membrane, or else a layer of gel.

The invention also provides a non-invasive method for the detection of a target substance by diffusion, comprising:

maintaining a detector means adjacent the surface of the skin of the subject, the detector means including at least one detector chemical contained in solution and capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin to produce a detectable signal, said detection occurring within the detector means;

the detector means further including a barrier means for substantially preventing migration of said detector chemical into the skin of the subject, the barrier means comprising either a microporous membrane containing covalent functional groups capable of covalently binding with the detector chemical contained in solution, or a permeable or a semipermeable membrane, or else a layer of gel.

The apparatus includes detector means and attachment means for maintaining the detector means adjacent to the surface of the skin of the subject. The detector means includes at least one detector chemical contained in solution and capable of chemically reacting with the target substance as the target substance migrates to the surface of the skin of the subject to produce a detectable signal, and barrier means for substantially preventing the detector chemical from migrating into the skin. The terminology "in solution" describes a uniformly dispersed mixture at the molecular or ionic level of one or more substances, the solute, in one or more other substances, the solvent, as is set forth in The Condensed Chemical Dictionary, 10th edition, G.G. Hawley, Van Nostrand Reinhold Co., 1981, pages 957-958. As is well known in the art, common types of solutions include liquid/liquid, solid/liquid and solid/solid systems. In accordance with the apparatus of the present invention, the detector means is maintained adjacent to the skin surface of the subject by the attachment means, and the detector chemical contained in solution in the detector means is capable of chemically reacting with the target substance as the target substance migrates to the surface of the skin of the subject in order to produce a detectable signal. Thus, the apparatus of the invention is not dependent on the collection of sweat

or other liquid transport medium in order to detect a target substance which migrates to the surface of the skin of a subject by diffusion. Additionally, the apparatus of the invention substantially prevents the detector chemical from migrating into the skin and avoids any toxic effects in the subject which would result from the detector chemical migrating the skin of the subject.

These and additional objects and advantages according to the present invention will become more apparent in view of the following detailed disclosure.

The following detailed description will be more fully understood in view of the Figure which sets forth one embodiment of the transdermal detection apparatus of the present invention.

As set forth above, the transdermal detection system of the present invention comprises an apparatus for the detection of a target substance which migrates to the surface of the skin of a subject by diffusion. The apparatus is particularly suitable for detecting a target substance which migrates to the surface of the skin of a subject by diffusion in the absence of a liquid transport medium such as sweat or interstitial fluid. The target substance may be any exogenous or endogenous chemical, or microbiological or biological material which has migrated to the surface of the skin by simple diffusion from within the body. The diffusion of the target substance need not be dependent on sweating or on collection of interstitial fluid.

The apparatus according to the invention comprises detector means including at least one detector chemical contained in solution and capable of chemically reacting with the target substance as the target substance migrates to the skin surface of the subject to produce a detectable signal. Depending on the target substance which is to be detected, the detector means may include a mixture of two or more detector chemicals contained in solution and capable of chemically reacting with the target substance as the target substance migrates to the surface of the skin of the subject to produce a detectable signal.

As set forth above, the term "in solution" refers to a uniformly dispersed mixture at the molecular or ionic level of one or more substances, the solute, in one or more other substances, the solvent. The detector chemical may comprise a chemical reagent such as an acid or a base, antibodies, enzymes, biological receptors, and/or mixtures thereof. The detector chemical may be in a liquid or solid state as long as it is contained in solution in a solvent as defined above. Preferred solvents comprise liquid aqueous solvents, for example, water or a saline solution, a gel or the like.

Suitable transdermal detection systems according to the present invention have been provided wherein the detector chemical provided in the detector means includes an oxidase enzyme contained in solution in an aqueous solvent. As is set forth in detail in the examples, a transdermal ethanol detection sys-

tem may be provided wherein the detector chemical includes alcohol oxidase and a transdermal glucose detection system may be provided wherein the detector chemical includes glucose oxidase. Additionally, the detector chemical may suitably comprise a mixture of an oxidase and a peroxidase in solution in an aqueous solvent. Horseradish peroxidase, for example, may be used in combination with an alcohol or glucose oxidase in a specific embodiment of the detector means of the present invention.

The detector chemical contained in the detector means is capable of chemically reacting with the target substance as the target substance migrates to the surface of the skin of the subject to produce a detectable signal. The detectable signal which results may be, for example, an optically detectable signal such as a visible color change or an electrically detectable signal such as a pH change, i.e. a change in the hydrogen ion concentration, or other ion concentration change. Other optically and electrically detectable signals which may result from the chemical reaction of the detector chemical with the target substance will be apparent to one skilled in the art and are included within the scope of the present invention.

The detector means of the present invention also includes a barrier means for substantially preventing the detector chemical from migrating into the skin of the subject. More particularly, the barrier means may comprise a microporous membrane containing covalent linking functional groups which covalently bind or link with the detector chemical to substantially prevent the detector chemical from migrating into the skin of the subject. Alternatively, the barrier means may comprise a permeable or semipermeable membrane which allows passage of the target substance therethrough while substantially preventing passage of the detector chemical to the skin surface of the subject and therefore substantially prevents migration of the detector chemical into the skin. A suitable permeable membrane may be formed of a permeable material such as tissue paper while a suitable semipermeable membrane may comprise a semipermeable material such as a dialysis membrane. A semipermeable membrane such as a dialysis membrane provides a more complete prevention of migration of the detector chemical into the skin than the permeable tissue membrane. Alternatively, the barrier means may comprise a layer of gel, for example, a silicone gel or other suitable gel, for substantially preventing the detector chemical from migrating into the skin of the subject. The barrier means is a particularly important component of the apparatus of the invention since the migration of various detector chemicals into the skin of a subject may cause a toxic reaction in the subject.

The apparatus according to the present invention also includes attachment means for maintaining the detector means adjacent to the surface of the skin of the subject. Because the detector means is adjacent

the surface of the skin of the subject, the detector chemical is available for chemically reacting with the target substance as the target substance migrates to the surface of the skin of the subject. The attachment means may comprise any components capable of maintaining the detector means adjacent the surface of the skin of the subject. In a preferred embodiment, the attachment means includes an adhesive area for adhesively maintaining the detector means adjacent to the surface of the skin of the subject. For example, one or more adhesive strips or an adhesive perimeter portion may be provided as the attachment means.

In one embodiment of the apparatus according to the present invention, the detector means further comprises a carrier which is saturated with the detector chemical contained in solution. Generally, the carrier acts as a physical support for the detector chemical contained in solution and is particularly suitable for use with solid/liquid solutions. The carrier may comprise a porous support member such as filter paper or the like or a microporous membrane similar to that described previously for use as the barrier means. For example, the carrier may comprise a microporous membrane containing covalent linking functional groups which covalently link or bind with the detector chemical to hold the detector chemical on the carrier. Thus, the carrier may also assist in preventing the detector chemical from migrating into the skin of the subject. The detector means comprising the carrier saturated with the detector chemical and the previously described barrier means, for example, a semipermeable or permeable membrane, are maintained adjacent the surface of the skin of the patient so that the detector chemical may chemically react with the target substance as the target substance migrates to the surface of the skin of the subject to produce a detectable signal. Collection of sweat or interstitial fluid containing the target substance is not necessary and, when a substantially saturated carrier is included in the detector means, sweat or interstitial fluid collection is not generally possible.

The apparatus according to the present invention may further include cover means for preventing loss of the detector chemicals from the apparatus and/or contamination of the apparatus from external environmental substances. For example, an impermeable cover means may be provided for covering the surfaces of the detector means which are not positionable adjacent the surface of the skin of the subject. Suitable impermeable cover means may comprise foil, an impermeable polymeric material or the like. Additionally, a removable impermeable cover means may be provided for covering the surface of the detector means which is positionable adjacent the surface of the skin of the subject. The removable cover serves to preserve the functionality of the detector chemicals and to prevent contamination of the apparatus during storage and prior to use. For example, a peel-

able foil or impermeable polymeric material may be provided on the surface of the detector means which is positionable adjacent the surface of the skin of the subject. The peelable material may then be removed from the apparatus prior to its use for the detection of a target substance migrating to the surface of the skin of the subject. In a preferred embodiment, removal of the removable impermeable cover exposes the detector means and the adhesive attachment means of the apparatus so that the adhesive means may then be applied to the skin surface for use of the apparatus in detecting a target substance.

The apparatus according to the invention may further include a signalling means which is capable of converting the detectable signal produced by the detector means into a form which is easily observable by the human eye. For example, a chemical compound may be included which is capable of reacting with the reaction product of the detector chemical and the target substance to produce a color change in a visible portion of the transdermal detection system. Furthermore, the signalling means may comprise a reflectance spectrometer for indicating a color change in the detector means or a pH or other electrode and meter for indicating a change in the hydrogen or other ion concentration in the detector means. Additionally, the signalling means may include a microprocessing unit for converting the detectable signal into a numerical measured value.

Attention is directed to the Figure which discloses one embodiment of the apparatus according to the present invention. The Figure discloses a transdermal detection apparatus 10 including detector means 12 and attachment means 14. The detector means 12 includes a porous carrier 16 formed of filter paper which is saturated with the detector chemical contained in solution and a barrier means 18 comprising a membrane material. The adhesive means 14 comprises an annular ring of a plastic polymeric material having an adhesive coating on its lower surface 20 which is adapted for positioning adjacent the surface of the skin of a subject. The apparatus further includes an impermeable cover 22 formed of an impermeable polymeric material which covers the surfaces of the detector means which are not positionable adjacent the surface of the skin of the subject. A removable impermeable cover 24 comprising a peelable material is also included in the apparatus and is adapted for removal from the apparatus prior to use for the detection of the target substance migrating to the surface of the skin of a subject. Once the cover 24 is removed from the apparatus, the adhesive surfaces 20 of the attachment means are positioned on the skin surface so that the detector means is maintained adjacent the surface of the skin of the subject, with barrier means 18 substantially preventing the detector chemical from migrating into the skin surface. The present invention will be more fully under-

stood in view of the following examples.

#### EXAMPLE 1

A transdermal ethanol detection system was prepared according to the present invention. The detector means comprised a carrier saturated with a mixture of detector chemicals contained in solution, and a barrier means for substantially preventing migration of the detector chemicals into the skin. Specifically, the carrier comprised a 5 x 7.5 mm. rectangular piece of filter paper (Whatman No. 40) saturated with a mixture of 1.1 units of an alcohol oxidase, 1 unit of horseradish peroxidase and 80 micrograms tetramethylbenzidine contained in solution in 30 ul of 0.04 Molar potassium phosphate monobasic-sodium phosphate dibasic buffer (pH 7.41) in 3% saline solution. The barrier means comprised a 1.1 cm. circular permeable membrane of Kimwipe™ material (supplied by Kimberly-Clark Corporation). An impermeable cover comprising Saran Wrap™ (supplied by Dow Chemical Co.) was also included. The attachment means comprised an annular disc member having adhesive on both sides (Double-Stick Disc™ supplied by 3M Corporation), a 1.25 31-75 mm inch outer diameter and an 11/32 8.7 mm inch inner aperture in which the detector means was positioned.

The transdermal ethanol detection system as described above may be attached to the skin surface of a subject in order to detect ethanol which migrates to the surface of the skin of a subject by diffusion. When the apparatus is placed on the skin surface, the detector means often turns from a light bluish-green color to a pale cream color. It is believed that this color change is caused by a change in the apparatus temperature from room temperature (23-25° C) to the skin surface temperature (30-32° C). The color will generally remain unchanged if no ethanol migrates to the skin surface of the subject. However, as ethanol migrates to the skin surface by diffusion, the detector means changes to an increasingly dark green to purple-blue color. For example, when attached to the skin of a person drinking alcohol at the rate of one and a half beers per hour, the detector means changed to a dark green-blue color within two to three hours after intake commencement. Additionally, the detector means has turned a green-blue color within 30 minutes of attaching the apparatus to the skin of a subject who has already consumed three or more beers at a rate of one and a half beers per hour. The color change was clearly visible to the naked eye while the apparatus was still attached to the subject. The color change was also measured by removing the detector means from the apparatus and measuring the decrease in reflectance of an infrared beam emitted at 940 NM in a reflectance spectrometer (Diascan Blood Glucose Self-Monitoring Meter supplied by Home Diagnostics Inc., Eatontown, N.J.). Relative to a control

specimen having no contact with ethanol, the apparatus registered a 5 to 30% unit decrease in percent transmittance of the infrared beam, the magnitude of the decrease depending upon the amount of ethanol which had been consumed by the subject. In this example, the target substance migrated to the skin surface by diffusion in the absence of sweat.

In the transdermal ethanol detection system of this example, the disclosed barrier means or the carrier may be replaced with a microporous membrane containing covalent linking functional groups. An example of such a membrane is the Pall Immunodyne Affinity Membrane supplied by Pall Biosupport Division, East Hills, N.J. The binding of the alcohol oxidase, horseradish peroxidase and tetramethylbenzidine to the microporous membrane assists in preventing migration of these components into the skin. Thus, the microporous membrane is a particularly suitable carrier or barrier means when a detector chemical is highly toxic to the subject on migration into the skin. The barrier means used above may also be replaced with a dialysis membrane such as the Spectra/Por 6 membranes supplied by Fischer Scientific, Silver Spring, MD (exhibiting a molecular weight cut off of 1000) which substantially prevents the detector chemicals which are unable to pass through the membrane from migrating into the skin.

## EXAMPLE 2

A transdermal glucose detection system according to the present invention is prepared wherein the detector means includes a porous carrier saturated with a mixture of glucose oxidase, horseradish peroxidase and tetramethylbenzidine contained in solution in a buffered saline solvent, and a barrier means. Specifically, the carrier comprises a 5 X 7.5 mm rectangular piece of filter paper (Whatman No. 40) impregnated with one unit of glucose oxidase, 1.5 units of horseradish peroxidase and 80 ug of tetramethylbenzidine contained in solution in 30 ul of 0.03 Molar sodium acetate buffer (pH of 5.2) in 3% saline. A barrier means comprising a membrane as set forth in Example 1 is included in the detector means, and the attachment means comprises an annular adhesive tape as described in Example 1. An impermeable plastic cover is also provided.

The transdermal glucose detection system may be attached to the skin surface of a subject for a predetermined time period, for example, six to twelve hours. Initially, the detector means will often turn from a light bluish-green color to a pale cream color. It is believed that this slight color change occurs as a result of the change in temperature of the apparatus from room temperature (23 - 25° C) to the temperature of the skin surface (30 - 32° C). When attached to the skin of a non-diabetic subject, the color of the detector means will remain a pale cream color or ex-

hibit only a slight color change to a very pale green. However, when attached to the skin surface of a diabetic subject, the color of the detector means will change to an increasingly dark green-blue color as glucose migrates to the skin surface. The color change could also be measured as set forth in Example 1 by measuring the decrease in reflectance of an infrared beam. The target substance will migrate to the skin surface by diffusion in the absence of sweat. As set forth in Example 1, the disclosed barrier means or carrier used in the present example may be replaced with a microporous membrane. The permeable membrane barrier means may also be replaced with a semipermeable membrane barrier layer.

The preceding examples are set forth to illustrate specific embodiments of the invention.

## Claims

1. An apparatus for the detection of a target substance which migrates to the surface of the skin of a subject by diffusion, comprising:
  - detector means (12) including at least one detector chemical contained in solution and capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject to produce a detectable signal; and
  - attachment means (14) for maintaining the detector means (12) adjacent the surface of the skin of the subject;
  - characterised in that:
    - the detector means (12) further comprises a barrier means (18) for substantially preventing said detector chemical from migrating into the skin of the subject, wherein the barrier means (18) comprises either a microporous membrane containing covalent functional groups capable of covalently binding with the detector chemical contained in solution, or a permeable or a semipermeable membrane, or else a layer of gel.
2. An apparatus as defined in claim 1, wherein the detector means (12) is capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject to produce an optically detectable signal.
3. An apparatus as defined by claim 2, wherein the detector means (12) is capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject to produce a visually detectable colour change in the detector means.
4. An apparatus as defined by claim 1, wherein the

detector means (12) is capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject to produce an electrically detectable signal.

5. An apparatus as defined by claim 4, wherein the detector means (12) is capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject to produce an electrically detectable change in an ion concentration in the detector means (12).
6. An apparatus as defined by any preceding claim, wherein the detector means (12) further comprises a carrier (16) substantially saturated with the detector chemical contained in solution and capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject.
7. An apparatus as defined by claim 6, wherein the carrier (16) comprises a porous support member.
8. An apparatus as defined by claim 7, wherein the carrier (16) comprises a microporous membrane containing covalent functional groups capable of covalently binding with the detector chemical contained in solution.
9. An apparatus as defined by any preceding claim, wherein the detector chemical is selected from chemical reagents, antibodies, enzymes and biological receptors and is contained in solution in a solvent.
10. An apparatus as defined by claim 9, wherein the detector chemical includes an oxidase contained in solution in a solvent.
11. An apparatus as defined by any of claims 1 to 8, wherein the detector means includes a mixture of detector chemicals contained in solution and capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin of the subject to produce a detectable signal.
12. An apparatus as defined by claim 11, wherein the detector chemical includes a mixture of an oxidase and a peroxidase in solution in an aqueous solvent.
13. An apparatus as defined by claim 10 or 12, wherein the oxidase is selected from alcohol oxidases and glucose oxidases.
14. An apparatus as defined by claim 12, wherein the peroxidase comprises horseradish peroxidase.
15. An apparatus as defined by any preceding claim, wherein the attachment means (14) includes an adhesive area for adhesively maintaining the detector means (12) adjacent the surface of the skin of the subject.
16. An apparatus as defined by any preceding claim, further comprising an impermeable cover means (22) covering the surfaces of the detector means (12) which are not positionable adjacent the surface of the skin of the subject.
17. An apparatus as defined by any preceding claim, further including a removable impermeable cover means (24) covering the surface of the detector means (12) which is positionable adjacent the surface of the skin of the subject, which removable cover means (24) is adapted to be removed from the apparatus prior to use for the detection of a target substance on migration to the surface of the skin of the subject.
18. An apparatus as defined by any preceding claim, further including a signalling means capable of converting the detectable signal produced by the detector means (12) into a form which is observable by the human eye.
19. An apparatus as defined by claim 18, wherein the signalling means includes microprocessing means.
20. An apparatus as defined by claim 1, wherein the target substance is ethanol, the detector means includes detector chemicals comprising an alcohol oxidase, horseradish peroxidase and tetramethylbenzidine, and wherein the detectable signal is a detectable colour change.
21. An apparatus as defined by claim 1, wherein the target substance is glucose, the detector means includes detector chemicals comprising glucose oxidase, horseradish peroxidase and tetramethylbenzidine, and wherein the detectable signal is a detectable colour change.
22. A non-invasive method for the detection of a target substance by diffusion, comprising maintaining a detector means (12) adjacent the surface of the skin of the subject, the detector means (12) including at least one detector chemical contained in solution and capable of chemically reacting with the target substance on the migration of the target substance to the surface of the skin to produce a detectable signal,

said detection occurring within the detector means;

the detector means (12) further including a barrier means (18) for substantially preventing migration of said detector chemical into the skin of the subject, said barrier means (18) comprising either a microporous membrane containing covalent functional groups capable of covalently binding with the detector chemical contained in solution, or a permeable or a semipermeable membrane, or else a layer of gel.

#### Patentansprüche

1. Vorrichtung für die Feststellung einer Targetsubstanz, die zu der Oberfläche der Haut einer Person durch Diffusion wandert, enthaltend: Detektormittel (12) mit mindestens einer in Lösung enthaltenen Detektor-Chemikalie, die in der Lage ist, chemisch mit der Targetsubstanz bei Migration der Targetsubstanz zu der Oberfläche der Haut der Person zur Erzeugung eines feststellbaren Signals zu reagieren; und Anbringungsmittel (14), um die Detektormittel (12) benachbart zu der Oberfläche der Haut der Person zu halten; dadurch gekennzeichnet, daß: das Detektormittel (12) weiterhin Barrierenmittel (18) aufweist, um die Detektor-Chemikalie im wesentlichen daran zu hindern, in die Haut der Person zu wandern, wobei die Barrierenmittel (18) entweder eine mikroporöse Membran mit kovalenten Funktionalgruppen, die einer kovalenten Bindung mit der in Lösung enthaltenen Detektor-Chemikalie fähig sind, oder eine permeable oder halbpermeable Membran oder eine Schicht Gel aufweisen.
2. Vorrichtung nach Anspruch 1, bei der die Detektormittel (12) in der Lage sind, chemisch mit der Targetsubstanz bei Migration der Targetsubstanz zu der Oberfläche der Haut der Person zur Erzeugung eines optisch feststellbaren Signals zu reagieren.
3. Vorrichtung nach Anspruch 2, bei der die Detektormittel (12) in der Lage sind, mit der Targetsubstanz bei der Migration der Targetsubstanz zu der Oberfläche der Haut der Person zur Erzeugung einer visuell feststellbaren Farbänderung in den Detektormitteln chemisch zu reagieren.
4. Vorrichtung nach Anspruch 1, bei der die Detektormittel (12) in der Lage sind, mit der Targetsubstanz bei der Migration der Targetsubstanz zu der Oberfläche der Haut der Person zur Erzeugung eines elektrisch feststellbaren Signals chemisch

zu reagieren.

5. Vorrichtung nach Anspruch 4, bei der die Detektormittel (12) in der Lage sind, mit der Targetsubstanz bei der Migration der Targetsubstanz zu der Oberfläche der Haut der Person zur Erzeugung einer elektrisch feststellbaren Änderung in einer Ionenkonzentration in den Detektormitteln (12) chemisch zu reagieren.
6. Vorrichtung nach einem vorhergehenden Anspruch, bei der die Detektormittel (12) weiterhin einen im wesentlichen mit der in Lösung enthaltenen Detektor-Chemikalie gesättigten Träger (16) aufweist, der in der Lage ist, chemisch mit der Targetsubstanz bei der Migration der Targetsubstanz zu der Oberfläche der Haut der Person zu reagieren.
7. Vorrichtung nach Anspruch 6, bei der der Träger (16) ein poröses Tragelement aufweist.
8. Vorrichtung nach Anspruch 7, bei der der Träger (16) eine mikroporöse Membran mit kovalenten Funktionalgruppen aufweist, die zu einer kovalenten Bindung mit der in Lösung enthaltenen Detektor-Chemikalie fähig sind.
9. Vorrichtung nach einem vorhergehenden Anspruch, bei der die Detektor-Chemikalie aus chemischen Reagenzien, Antikörpern, Enzymen und biologischen Rezeptoren ausgewählt und in Lösung in einem Lösungsmittel enthalten ist.
10. Vorrichtung nach Anspruch 9, bei der die Detektor-Chemikalie eine in Lösung in einem Lösungsmittel enthaltene Oxidase umfaßt.
11. Vorrichtung nach einem der Ansprüche 1 bis 8, bei der die Detektormittel eine Mischung aus in Lösung enthaltenen Detektorchemikalien aufweist, die in der Lage sind, mit der Targetsubstanz bei der Migration der Targetsubstanz zu der Oberfläche der Haut der Person zur Erzeugung eines feststellbaren Signals chemisch zu reagieren.
12. Vorrichtung nach Anspruch 11, bei der die Detektor-Chemikalie eine Mischung aus einer Oxidase und einer Peroxidase in Lösung in einem wäßrigen Lösungsmittel umfaßt.
13. Vorrichtung nach Anspruch 10 oder 12, bei der die Oxidase aus Alkoholoxidasen und Glukoseoxidasen ausgewählt ist.
14. Vorrichtung nach Anspruch 12, bei der die Peroxidase Meerrettichperoxidase umfaßt.



15. Vorrichtung nach einem vorhergehenden Anspruch, bei der die Anbringungsmittel einen Kleb-  
bereich zum Klebehalten der Detektormittel  
(12) benachbart der Oberfläche der Haut der  
Person enthalten. 5
16. Vorrichtung nach einem vorhergehenden An-  
spruch, weiterhin enthaltend undurchlässige Ab-  
deckmittel (22), die die Oberflächen der Detek-  
tormittel (12) abdecken, die nicht benachbart der  
Oberfläche der Haut der Person positionierbar  
sind. 10
17. Vorrichtung nach einem vorhergehenden An-  
spruch, weiterhin enthaltend abnehmbare un-  
durchlässige Abdeckmittel (24), die die Oberflä-  
che der Detektormittel (12) abdecken, die be-  
nachbart der Oberfläche der Haut der Person po-  
sitionierbar sind, wobei die abnehmbaren Ab-  
deckmittel (24) sich von der Vorrichtung vor ihrer  
Verwendung für die Feststellung einer Target-  
substanz bei der Migration zu der Oberfläche der  
Haut der Person entfernen lassen. 15
18. Vorrichtung nach einem vorhergehenden An-  
spruch, weiterhin enthaltend Signalisierungsmi-  
tel, die in der Lage sind, das von den Detektormi-  
teln (12) erzeugte feststellbare Signal in eine  
Form umzuwandeln, die von dem menschlichen  
Auge feststellbar ist. 20
19. Vorrichtung nach Anspruch 18, bei der die Signa-  
lisierungsmittel Mikroprozessormittel enthalten. 25
20. Vorrichtung nach Anspruch 1, bei der die Target-  
substanz Ethanol ist, die Detektormittel Detektor-  
Chemikalien unter Einschluß einer alkoholischen  
Oxidase, Meerrettichperoxidase und Tetrame-  
thylbenzidin umfassen, und bei der das feststell-  
bare Signal eine feststellbare Farbänderung ist. 30
21. Vorrichtung nach Anspruch 1, bei der die Target-  
substanz Glukose ist, die Detektormittel Detek-  
tor-Chemikalien unter Einschluß von Glukoseoxi-  
dase, Meerrettichperoxidase und Tetramethyl-  
benzidin umfassen, und bei der das feststellbare  
Signal eine feststellbare Farbänderung ist. 35
22. Nicht invasives Verfahren für die Feststellung ei-  
ner Targetsubstanz durch Diffusion, bei dem De-  
tektormittel (12) benachbart der Oberfläche der  
Haut der Person gehalten werden, die minde-  
stens eine in Lösung enthaltene Detektor-Chemi-  
kalie enthalten, die in der Lage ist, mit der Target-  
substanz bei der Migration der Targetsubstanz zu  
der Oberfläche der Haut chemisch zu reagieren,  
zur Erzeugung eines feststellbaren Signals, wo-  
bei die Feststellung in den Feststellmitteln auf-  
tritt, bei dem die Detektormittel (12) weiterhin  
Barrierenmittel (18) aufweisen, um im wesentli-  
chen die Migration der Detektor-Chemikalie in  
die Haut der Person zu verhindern, und die Bar-  
rierenmittel (18) entweder eine mikroporöse  
Membran mit kovalenten Funktionalgruppen, die  
einer kovalenten Bindung mit der in Lösung ent-  
haltenen Detektor-Chemikalie fähig sind, oder ei-  
ne permeable oder eine semipermeable Mem-  
bran oder eine Schicht Gel enthalten. 40

## Revendications

- Dispositif pour détecter une substance cible qui migre par diffusion à la surface de la peau d'un sujet, comportant:  
des moyens (12) formant détecteur comportant au moins une substance chimique formant détecteur contenue dans une solution et capable de réagir chimiquement avec la substance cible lors de la migration de la substance cible à la surface de la peau du sujet pour produire un signal pouvant être détecté, et  
des moyens (14) de fixation destinés à maintenir les moyens (12) formant détecteur adjacents à la surface de la peau du sujet, caractérisé en ce que:  
les moyens (12) formant détecteur comportent en outre des moyens formant barrière (18) pour empêcher pratiquement ladite substance chimique formant détecteur de migrer jusqu'à la peau du sujet, dans lequel les moyens formant barrière (18) sont constitués soit d'une membrane micro-poreuse contenant des groupes fonctionnels covalents capables d'être liés de manière covalente à la substance chimique formant détecteur contenue dans la solution, soit une membrane perméable, soit une membrane semi-perméable, ou encore une couche de gel. 45
- Dispositif selon la revendication 1, dans lequel les moyens formant détecteur (12) sont capables de réagir chimiquement avec la substance cible lors de la migration de la substance cible à la surface de la peau du sujet pour produire un signal pouvant être détecté de manière optique. 50
- Dispositif selon la revendication 1 ou 2, dans lequel les moyens formant détecteur (12) sont capables de réagir chimiquement avec la substance cible lors de la migration de la substance cible à la surface de la peau du sujet pour produire un changement de couleur pouvant être détecté visuellement dans les moyens formant détecteur. 55
- Dispositif selon la revendication 1, dans lequel les moyens formant détecteur (12) sont capables

de réagir chimiquement avec la substance cible lors de la migration de la substance cible vers la surface de la peau du sujet pour produire un signal pouvant être détecté de manière électrique.

5. Dispositif selon la revendication 4, dans lequel les moyens formant détecteur (12) sont capables de réagir chimiquement avec la substance cible lors de la migration de la substance cible vers la surface de la peau du sujet pour produire un changement pouvant être détecté électriquement de la concentration ionique des moyens formant détecteur (12).
6. Dispositif selon l'une quelconque des revendications précédentes, dans lequel les moyens formant détecteur (12) comportent en outre un support (16) pratiquement saturé par la substance chimique formant détecteur contenue en solution et capable de réagir chimiquement avec la substance cible lors de la migration de la substance cible vers la surface de la peau du sujet.
7. Dispositif selon la revendication 6, dans lequel le support (16) est constitué d'un élément de support poreux.
8. Dispositif selon la revendication 7, dans lequel le support (16) est constitué d'une membrane poreuse contenant des groupes fonctionnels covalents capables d'être liés de manière covalente à la substance chimique formant détecteur contenue dans la solution.
9. Dispositif selon l'une quelconque des revendications précédentes, dans lequel la substance chimique formant détecteur est sélectionnée parmi des réactifs chimiques, des anticorps, des enzymes et des récepteurs biologiques et est contenue en solution dans un solvant.
10. Dispositif selon la revendication 9, dans lequel la substance chimique formant détecteur comporte une oxydase contenue en solution dans un solvant.
11. Dispositif selon l'une quelconque des revendications 1 à 8, dans lequel les moyens formant détecteur comportent un mélange de substances chimiques formant détecteur contenues en solution et capable de réagir chimiquement avec la substance cible lors de la migration de la substance cible vers la surface de la peau du sujet pour produire un signal pouvant être détecté.
12. Dispositif selon la revendication 11, dans lequel la substance chimique formant détecteur comporte un mélange d'une oxydase et d'une pe-

roxidase en solution dans un solvant aqueux.

13. Dispositif selon la revendication 10 ou 12 dans lequel l'oxydase est choisi parmi les alcool oxydases et les glucose oxydases.
14. Dispositif selon la revendication 12, dans lequel le peroxydase est constitué de peroxydase de raifort.
15. Dispositif selon l'une quelconque des revendications précédentes, dans lequel les moyens de fixation (14) comportent une zone adhésive pour maintenir de manière adhésive les moyens formant détecteur (12) adjacents à la surface de la peau du sujet.
16. Dispositif selon l'une quelconque des revendications précédentes, comportant en outre des moyens (22) formant couvercle imperméable recouvrant les surfaces des moyens formant détecteur (12) qui ne peuvent pas être positionnées adjacentes à la surface de la peau du sujet.
17. Dispositif selon l'une quelconque des revendications précédentes, comportant en outre des moyens (24) formant couvercle imperméable amovible recouvrant la surface des moyens formant détecteur (12) qui peut être positionnée adjacente à la surface de la peau du sujet, lesquels moyens (24) formant couvercle amovible sont adaptés pour être enlevés du dispositif avant qu'il ne soit utilisé pour détecter une substance cible migrant vers la surface de la peau du sujet.
18. Dispositif selon l'une quelconque des revendications précédentes, comportant en outre des moyens de signalisation capables de convertir le signal pouvant être détecté produit par les moyens formant détecteur (12) sous une forme qui peut être observée par l'oeil humain.
19. Dispositif selon la revendication 18, dans lequel les moyens de signalisation comportent des moyens formant microprocesseur.
20. Dispositif selon la revendication 1, dans lequel la substance cible est l'éthanol, les moyens formant détecteur comportent des substances chimiques formant détecteur constituées d'alcool oxydase, de peroxydase du raifort et de tétraméthylbenzidine, et dans lequel le signal pouvant être détecté est un changement de couleur pouvant être détecté.
21. Dispositif selon la revendication 1, dans lequel la substance cible est le glucose, les moyens formant détecteur comportent des substances chi-

miques formant détecteur constituées de glycol oxydase, de peroxydase du raifort et de tétraméthylbenzidine, et dans lequel le signal pouvant être détecté est un changement de couleur pouvant être détecté.

5

22. Procédé non invasif destiné à la détection d'une substance cible par diffusion, comportant les étapes consistant à:

maintenir des moyens formant détecteur (12) adjacents à la surface de la peau du sujet, les moyens formant détecteur (12) comportant au moins une substance chimique formant détecteur contenue en solution et capable de réagir chimiquement avec la substance cible lors de la migration de la substance cible vers la surface de la peau pour produire un signal pouvant être détecté, ladite détection survenant à l'intérieur des moyens formant détecteur,

10

15

les moyens formant détecteur (12) comportant en outre des moyens formant barrière (18) pour empêcher pratiquement la migration de ladite substance chimique formant détecteur jusque dans la peau du sujet, lesdits moyens formant barrière (18) étant constitués soit d'une membrane micro-poreuse contenant des groupes fonctionnels covalents capables de se lier de manière covalente à la substance chimique formant détecteur contenue en solution, soit d'une membrane perméable ou semi-perméable, ou encore d'une couche de gel.

20

25

30

35

40

45

50

55

